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Eradication of Small Intestinal Bacterial Overgrowth Reduces Symptoms of Irritable Bowel Syndrome

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OBJECTIVES: Irritable bowel syndrome is the most common gastrointestinal diagnosis. The symptoms of irritable bowel syndrome are similar to those of small intestinal bacterial overgrowth. The purpose of this study was to test whether overgrowth is associated with irritable bowel syndrome and whether treatment of overgrowth reduces their intestinal complaints.

METHODS: Two hundred two subjects in a prospective database of subjects referred from the community undergoing a lactulose hydrogen breath test for assessment of overgrowth were Rome I criteria positive for irritable bowel syndrome. They were treated with open label antibiotics after positive breath test. Subjects returning for follow-up breath test to confirm eradication of overgrowth were also assessed. Subjects with inflammatory bowel disease, abdominal surgery, or subjects demonstrating rapid transit were excluded. Baseline and after treatment symptoms were rated on visual analog scales for bloating, diarrhea, abdominal pain, defecation relief, mucous, sensation of incomplete evacuation, straining, and urgency. Subjects were blinded to their breath test results until completion of the questionnaire.

RESULTS: Of 202 irritable bowel syndrome patients, 157 (78%) had overgrowth. Of these, 47 had follow-up testing. Twenty-five of 47 follow-up subjects had eradication of small intestinal bacterial overgrowth. Comparison of those that eradicated to those that failed to eradicate revealed an improvement in irritable bowel syndrome symptoms with diarrhea and abdominal pain being statistically significant after Bonferroni correction ($p < 0.05$). Furthermore, 48% of eradicated subjects no longer met Rome criteria ($\chi^2 = 12.0$, $p < 0.001$). No difference was seen if eradication was not successful.

CONCLUSIONS: Small intestinal bacterial overgrowth is associated with irritable bowel syndrome. Eradication of the overgrowth eliminates irritable bowel syndrome by study criteria in 48% of subjects. (Am J Gastroenterol 2000;95: 3503–3506. © 2000 by Am. Coll. of Gastroenterology)

INTRODUCTION

Irritable bowel syndrome (IBS) is the most common diagnosis in gastroenterology. Prevalence rates are reported to be as high as 30% in the general population (1, 2) and functional bowel complaints (including IBS) are responsible for up to 50% of visits to the gastroenterologist (3). Despite this high prevalence, the cause of IBS is unknown.

The diagnostic criteria for IBS include symptoms of bloating, abdominal pain, and altered bowel habits (4). These symptoms are similar to those experienced by subjects with small intestinal bacterial overgrowth (SIBO) (5). Using breath testing techniques, studies have demonstrated an association between SIBO and IBS. When Galatola *et al.* (6) performed ^{14}C-xylose breath tests on subjects with a number of gastrointestinal disorders, the prevalence of abnormal breath tests demonstrating SIBO was 56% and 29% in diarrhea and constipation predominant IBS, respectively. This was used to suggest a poor sensitivity and specificity for breath testing. However, Nayak *et al.* (7) demonstrated that IBS subjects treated with metronidazole were significantly better than placebo-treated patients, suggesting that bacteria may play a role in the symptoms of IBS. To date, there is no information on the effect of eradication of SIBO on the symptoms of IBS.

In this study, we aim to test the hypotheses that the prevalence of SIBO is high in IBS subjects referred for lactulose hydrogen breath testing and that eradication of SIBO with antibiotic treatment improves the gastrointestinal symptoms of IBS.

MATERIALS AND METHODS

Patient Population and Questionnaire

All patients consecutively referred to the GI Motility Program at the Cedars-Sinai Medical Center for a lactulose hydrogen breath test (LHBT) were given a questionnaire (8). Information from the completed questionnaires was entered into a database. The questionnaire involved rating Rome I IBS symptoms including bloating, diarrhea, abdominal pain, defecation relief, passage of mucous, sensation of incomplete evacuation, straining, and urgency on a scale ranging from 0 to 5, with 0 representing absence of the symptom. Subjects were blinded to the results of the LHBT until completion of the questionnaire. From these bowel symptoms and duration of complaints, subjects meeting Rome I criteria (4) for IBS were identified. Subjects with a history of inflammatory bowel disease or abdominal surgery were excluded as these subjects have an increased risk of developing SIBO. Subjects demonstrating rapid transit on the LHBT were also excluded. Rapid transit was defined based on the following criteria: 1) a single peak representing colonic flora and 2) hydrogen production <90 min after ingestion of lactulose. All procedures used in this study were approved by the Institutional Review Board at Cedars-Sinai Medical Center, Los Angeles, California.

Lactulose Hydrogen Breath Test

All subjects presented to the GI Motility Laboratory at Cedars-Sinai Medical Center for LHBT after an 8-h fast. Subjects then ingested 10 g of lactulose syrup (Inalco Spa, Milano, Italy, packaged by Xactdose Inc., South Beloit, IL) after a sample of their breath was collected at baseline. Further breath samples were then obtained every 15 min for 3 h. All breath samples were end-expiratory and analyzed immediately by a model DP Quintron gas chromatograph (Quintron Instrument Company, Milwaukee, WI). The concentration of breath hydrogen was measured in parts per million. The measurements were then plotted graphically and analyzed. The diagnosis of SIBO was confirmed based on the following criteria: 1) two distinct peaks representing small intestinal (early peak) and colonic (late peak) flora (9), 2) hydrogen production <90 min after ingestion of lactulose, and 3) an absolute change in hydrogen concentration of >20 ppm (10). Eradication of SIBO was confirmed when the post-treatment LHBT no longer met the above criteria.

Antibiotic Treatment

Subjects diagnosed with SIBO by the LHBT were given a 10-day course of antibiotics at the discretion of their physician (*e.g.,* Neomycin, ciprofloxacin, flagyl, or doxycyline) to eradicate their bacterial overgrowth. Those referred back for a follow-up LHBT approximately 7–10 days after completion of the antibiotics were given a second questionnaire. Once again the subjects were blinded to the results of the LHBT until the questionnaire was completed.

Data Analysis

The results of the LHBT were analyzed. The maximal late peak of hydrogen was compared before and after treatment using a paired *t* test. In addition, the treated subjects were divided into two groups, those who had incomplete eradication after treatment (not eradicated) and those who achieved complete eradication of their SIBO (eradicated). The concentration of hydrogen produced at each of the 15-min intervals for the before treatment, not eradicated, and eradicated groups was plotted against time and the area under the curve was calculated by the trapezoidal rule. The areas were then compared by a one-way analysis of variance. Furthermore, a comparison of the percent change in hydrogen concentration before and after treatment for the maximal late peak concentration was performed between the not eradicated and the eradicated group using a *t* test.

Table 1. Patient Demographics

	Total Group [No. (%)] (n = 202)	SIBO [No. (%)] (n = 157)	No SIBO [No. (%)] (n = 45)
Age*	41.9 ± 15.2	42.8 ± 14.8	38.6 ± 16.1
Sex†			
Men	47 (23.3)	32 (20.4)	15 (33.3)
Women	155 (76.7)	125 (79.6)	30 (66.7)
Smoke†			
Previously	77/200 (38.5)	60 (38.2)	17/43 (39.5)
Currently	12/200 (6.0)	11 (7.0)	1/43 (2.2)
Alcohol†	113 (56.8)‡	87 (56.1)§	26 (59.1)‖

* Data are mean ± standard deviation, analyzed by *t* test.
† Analyzed by χ^2.
‡ Only 199 subjects responded to the question.
§ Only 155 subjects responded to the question.
‖ Only 44 subjects responded to the question.
p = not significant.

A McNemar's test was used to compare the presence of symptoms before and after treatment in IBS subjects with successful and unsuccessful eradication of SIBO. For a symptom to be absent, the subject had to place a zero for severity of that symptom. To adjust for the measurement of eight variables, a Bonferroni correction was used. This established that for any variable to be significant the *p* value had to be ≤ 0.006. McNemar's test was also performed to assess the number of subjects meeting Rome criteria for IBS before treatment and in the eradicated group and not eradicated group.

RESULTS

Patient Population

Questionnaires from the 448 subjects were entered into the database. Of this group, 202 subjects met Rome criteria for IBS after exclusion criteria were met. Two hundred forty-six subjects were excluded. These included subjects with IBD (n = 72), abdominal surgery (n = 40), rapid transit (n = 5), and those who did not meet Rome criteria (n = 129). Of the 202 IBS subjects, 157 (78%) had a positive LHBT suggesting SIBO. The demographics for the total group, including those with and without SIBO are presented in Table 1. No difference in demographics was found between IBS subjects with SIBO and those with no SIBO.

Breath Hydrogen Response to Treatment

Of the 157 subjects treated with antibiotics, 47 were referred for a follow-up LHBT to confirm eradication of their SIBO. Of these subjects, 25 achieved complete and 22 incomplete eradication of their SIBO. Antibiotic treatment significantly reduced hydrogen production from 68.0 ± 35.5 ppm to 35.0 ± 29.1 ppm ($p < 0.00001$) in the 47 subjects. A significantly greater reduction in hydrogen production was seen at all time points in subjects whose SIBO was completely eradicated. Figure 1 illustrates the mean hydrogen

Table 2. A Comparison of the Presence of Individual Rome Criteria Symptoms Before and After Treatment in Subjects with IBS With Successful and Unsuccessful Eradication of SIBO

	Not Eradicated (n = 22)				Eradicated (n = 25)			
Symptom	Before (n)	After (n)	χ^2*	*p* Value†	Before (n)	After (n)	χ^2*	*p* Value†
Bloating	18	17	0.3	NS	24	18	4.5	NS
Diarrhea	16	11	5.0	NS	21	13	8.0	<0.05
Abd pain	22	19	3.0	NS	25	14	11.0	<0.001
Def relief	18	15	3.0	NS	17	13	2.7	NS
Mucous	8	9	0.1	NS	10	6	2.0	NS
Inc. evac	19	18	0.2	NS	18	17	0.2	NS
Straining	15	16	0.3	NS	12	11	0.1	NS
Urgency	18	16	1.0	NS	16	13	1.8	NS

Abd Pain = abdominal pain; Def Rel = abdominal pain relieved with defecation; Inc. Evac = incomplete evacuation.

* χ^2 (McNemar's Test) before Bonferroni correction.

† *p* value after Bonferroni correction.

concentration *versus* time for subjects in the before treatment group, the not eradicated group, and the eradicated group. Antibiotic treatment significantly reduced the area under the curve for both after treatment groups ($p < 0.0001$). In addition, hydrogen production for the maximal late peak decreased by 68.5 ± 15.6% in the eradicated group, but only 9.6 ± 60.9% in the not eradicated group ($p < 0.0001$).

The antibiotics used in the treatment of SIBO in the 47 subjects were neomycin (n = 24), ciprofloxacin (n = 2), flagyl (n = 3), doxycycline (n = 1), and unknown (n = 17).

Symptom Response to Treatment

When the actual presence of symptoms was compared, successful eradication of SIBO significantly reduced the number of subjects complaining of bloating, diarrhea, and abdominal pain (Table 2). Even after Bonferroni correction for eight variables, diarrhea and abdominal pain were still significantly eliminated with SIBO eradication. No difference was seen in the not eradicated group.

When comparing the number of subjects meeting Rome criteria before and after therapy, 48% of subjects achieving successful eradication no longer met Rome criteria for IBS ($p < 0.001$). No difference was seen if SIBO eradication was unsuccessful (Table 3).

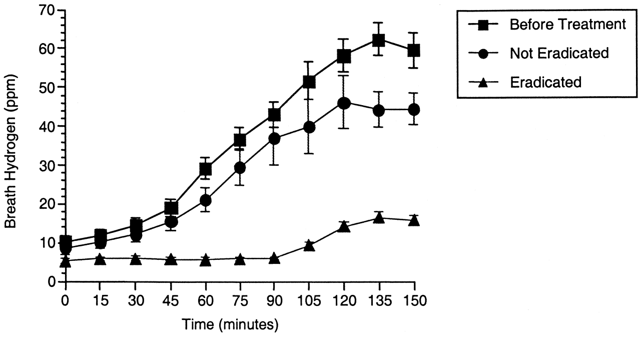

Figure 1. Hydrogen production in IBS subjects in the total before treatment group, the not eradicated group, and the eradicated group.

DISCUSSION

In this study, we find that subjects with IBS appear to have a high prevalence of SIBO as demonstrated by LHBT. Treatment of SIBO with antibiotics appears to have a significant improvement in symptoms and converts many IBS patients from Rome criteria positive to negative. This is the first study to show that eradication of SIBO improves the gastrointestinal symptoms of IBS.

Two previous citations are consistent with the findings of this paper. Galatola *et al.* (6) determined that up to 56% of subjects with IBS had a positive ^{14}C-xylose breath test. Although they viewed their observation as suggesting the breath test may be unreliable, as it was positive in so many patients, the possibility that IBS had an increased prevalence of SIBO was not pursued. Our findings of a 78% association would support, instead, this alternative explanation for Galatola's study. Furthermore, Nayak *et al.* (7) conducted a double-blind trial of flagyl *versus* placebo in a group of symptomatic Indian IBS-like subjects in the absence of identifiable stool pathogens. They showed that during a prolonged period of time after treatment, flagyl resulted in highly significant improvement in gastrointestinal complaints over placebo. Our study extended these two observations by assessing the prevalence of SIBO (by LHBT) in a group of IBS subjects referred for breath testing and showed that Rome criteria symptoms of IBS improved with open label treatment with antibiotics.

Table 3. Comparison of Rome Criteria-Positive Subjects Before and After Treatment With Successful and Unsuccessful Eradication of SIBO

	Before Treatment	After Treatment	Total	χ^2	*p* Value
Not eradicated					
Rome +	22	18	40		
Rome −	0	4	4		
Total eradicated	22	22	44	4.0	0.05
Rome +	25	13	38		
Rome −	0	12	12		
Total	25	25	50	12.0	<0.001

The response seen in Table 3 was unlikely to be a placebo effect as there was a striking difference between the eradicated and not eradicated groups and both sets of patients were treated. Whether or not subjects achieved eradication of SIBO (as determined by LHBT) with the prescribed antibiotic, they were blinded to the result of the LHBT during the completion of the follow-up questionnaire. Eradication was achieved in 53% of subjects. Because a significantly greater degree of improvement was reported in subjects achieving eradication of SIBO compared to those who failed to eradicate, even as they were blinded to the outcome after treatment, this difference strongly supports a specific benefit of SIBO eradication. In addition, graded response between eradicated and not eradicated is unlikely to represent a placebo response. Eradication of SIBO significantly eliminated symptoms of diarrhea and abdominal pain, whereas none of the symptoms studied could be eliminated in the group that did not achieve eradication (Table 3). When Rome criteria were put to the test, 48% of eradicated subjects no longer met Rome criteria (by definition, achieving cure). To our knowledge, no study has previously described a therapeutic modality that succeeds in achieving elimination of IBS by study definitions.

One limitation of the study is the small number of subjects returning for follow-up LHBT. Two explanations are possible. The first is that subjects did not feel better after initial antibiotic treatment and therefore, either refused to have or physicians refused to entertain the possibility of incomplete eradication. The second alternative is that the subjects not returning actually had a good response resulting in the referring physician believing that a second breath test was unnecessary. Given the internal education of our referral base, we believe that the latter is more likely. If so, this would have potentially underestimated the response and treatment success rates observed here. However, there are no data to substantiate this.

Another issue with the study is that the diagnosis of SIBO was based on the LHBT. The sensitivity of the LHBT in diagnosing SIBO is reported to be between 16% and 61% (11, 12). The problem with this assessment of the LHBT is that it was compared to duodenal and jejunal aspirates. Direct culture is considered by some to be the gold standard. There is now mounting evidence that direct culture may not be adequate. Direct culture is fraught with difficulty including oral contamination during collection (13). Furthermore, direct culture has a reproducibility of 38% compared to 92% for breath testing (14). Another major problem with direct culture is that sampling is restricted to the proximal small intestine. In the absence of hypochlorhydia, most SIBO results from proximal migration of colonic flora and therefore, would intuitively result in substantially higher levels of bacteria in distal small bowel. Sampling of this area is difficult. A nondigestible sugar such as lactulose allows determination of SIBO in all areas of potential involvement.

In summary, there appears to be an increased prevalence of SIBO in subjects with IBS referred for LHBT. Successful treatment of SIBO in this group results in a significant improvement in gastrointestinal complaints with elimination of IBS (as defined by Rome criteria) in almost 50% of subjects that cannot be explained by placebo affect alone. Controlled studies are needed to further investigate this phenomenon.

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